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Research Article

Identification of lymphatic drainage and lymph nodes of the mammary gland in cats using patent blue dye: A post-mortem study

Identificação da drenagem linfática e dos linfonodos da glândula mamária em gatos utilizando corante azul patente: Um estudo post-mortem

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ABSTRACT

Similar to other species, lymph nodes are the primary metastatic site for mammary gland tumors in cats. Although lymphography is a useful tool for identifying regional and sentinel lymph nodes in oncology, it remains underused in veterinary medicine due to unawareness and financial restraints. Patent blue dye is the most commonly used vital dye for visualizing lymph nodes during surgery in dogs and cats. This study aimed to identify and describe the lymphatic drainage of mammary glands, axillary, and superficial inguinal lymph nodes in cats using 2.5% patent blue dye. The dye was administered post-mortem to specific mammary glands of 13 female cats. The lymph nodes were then examined for number, size, anatomic location, and macroscopic characteristics, and further evaluated through histopathology. The dye successfully marked the lymph nodes in 92.3% of cases (12 out of 13), staining 32 lymph nodes. Notable anatomical variations were observed, with 38.5% of cats presenting two axillary lymph nodes, and only one superficial inguinal lymph node identified per cat. Patent blue dye proved to be an efficient technique for locating lymph nodes involved in the lymphatic drainage of mammary glands in female cats.

KEYWORDS: Lymph center. Axillary. Inguinal. Oncology. Feline.

RESUMO

Semelhante a outras espécies, os linfonodos são o principal local de metástase dos tumores de glândulas mamárias em gatos. Embora a linfografia seja uma ferramenta útil para identificar linfonodos regionais e sentinelas na oncologia, ainda é subutilizada na medicina veterinária por desconhecimento das técnicas e custos. O corante azul patente é o mais comumente utilizado para a visualização transcirúrgica de linfonodos em cães e gatos. Este estudo visou identificar e descrever a drenagem linfática das glândulas mamárias, linfonodos axilares e inguinais superficiais em gatos, usando corante azul patente a 2,5%. O corante foi administrado post-mortem em glândulas mamárias específicas de 13 gatas. Os linfonodos foram então examinados quanto ao número, tamanho, localização anatômica e características macroscópicas, sendo ainda avaliados histopatologicamente. O corante marcou com sucesso os linfonodos em 92,3% dos casos (12 de 13), corando 32 linfonodos. Foram observadas variações anatômicas notáveis, com 38,5% dos gatos apresentando dois linfonodos axilares, e apenas um linfonodo inguinal superficial identificado por gato. O corante azul patente provou ser uma técnica eficiente para localizar linfonodos envolvidos na drenagem linfática das glândulas mamárias em gatas.

PALAVRAS-CHAVE: Centro linfático. Axilar. Inguinal. Oncologia. Felino.

INTRODUCTION

Mammary gland tumors (MGTs) are among the most commonly diagnosed neoplasms in cats (CASSALI et al. 2020). The frequency of malignant MGTs in this species varies from 80% to 96%, with adenocarcinomas being the most common histological type (MILLS et al. 2015). Similar clinical-pathological and genetic characteristics between mammary gland cancer in cats and women are observed, including the highest incidence in elderly patients, histological subtypes, biological behavior, and a pattern of metastasis to the lungs and lymph nodes (LNs) (CASSALI et al. 2018). Standard prognostic factors in the cat also include histopathologic grade and regional/distant metastasis (VAN DE VIJVER et al. 2002). It offers a significant comparative viewpoint in oncology that enhances comprehension of mammary gland cancer biology. Recent studies aim to drive progress in therapeutic approaches and improve survival rates (ADEGA et al. 2016).

Felines affected with MGTs and concurrent nodal metastasis had a shorter survival time compared to individuals without LN impairment (ZAPPULLI et al. 2015). Although LN excision is clinically significant in feline oncology, detailed evidence remains scarce, with few studies exploring its impact on prognosis and treatment outcomes. Despite recommendations to use patent blue dye in this context, comprehensive investigations employing this technique are limited (CASSALI et al. 2018).

Among vital dyes, patent blue is the most used in veterinary medicine, particularly helpful for the intraoperative identification of axillary LNs, essential for staging patients with MGTs (BIANCHI et al. 2018). Direct or indirect lymphography consists of the visualization of the lymphatic drainage using radiopharmaceuticals (lymphoscintigraphy) or contrast agents, such as lipiodol, in conjunction with imaging techniques (e.g. radiography and computed tomography) (COLLIVIGNARELLI et al. 2021), with increasingly use over recent decades in small animal oncology (BIANCHI et al. 2018, COLLIVIGNARELLI et al. 2021, TUOHY et al. 2009). The sentinel LN represents the first LN to receive lymphatic drainage from a solid tumor (CHITI et al. 2022). Thus, this study aimed to assess the lymphatic drainage of the mammary gland, with special emphasis on the axillary and superficial inguinal lymph nodes in cats using the patent blue dye.

MATERIALS AND METHODS

Study Overview

A post-mortem experimental study was conducted at the Veterinary Hospital of Universidade Federal de Minas Gerais (VH-UFMG) from January-December of 2022. Inclusion criteria included the following: fresh cadavers (dead within 24 hours of time of the analysis) with intact cutaneous and subcutaneous skin tissues, and no previous clinical history of neoplasms. Cadavers were obtained from VH-UFMG and private veterinary clinics in Belo Horizonte, Minas Gerais, Brazil. Exclusion criteria consisted in cadavers with a freezing time of more than 24 hours, and overt abdominal ventral skin/mammary lesions (e.g. mastitis, tumors in mammary chains, and enlarged superficial LNs) were excluded from this study.

The project received approval from the Ethics Committee on Animal Use at

UFMG (125/2022), and all cases included an authorization term signed by the owner. Regarding the stablished criteria, 13 cats were selected for the study. The flow diagram below (Figure 1) illustrates key points of our methods. Contralateral mammary gland drainage was not the focus of this study; only ipsilateral drainage was analyzed.

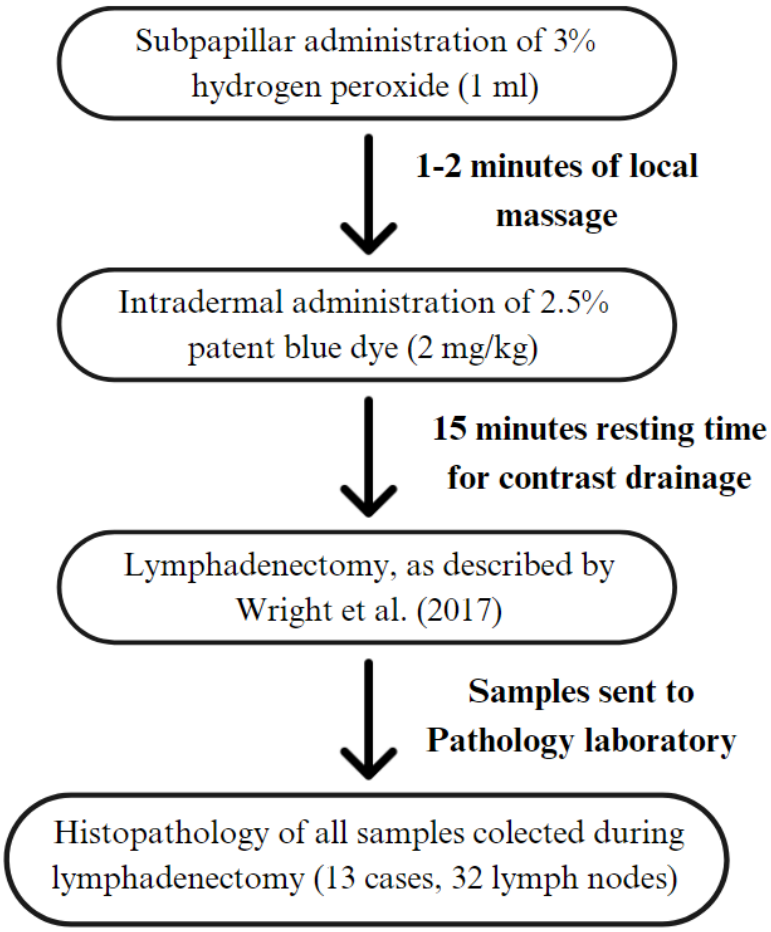

Figure 1. Flow diagram illustrating the key stages of our study in identifying LNs draining feline mammary glands.

Patent blue dye administration

Hydrogen peroxide was administered subpapillary to dilate lymphatic vessels, following a local massage for one to two minutes. Then, 2.5% patent blue dye was administered in 3 ml syringes with a 25 G needle attached, intradermally, in two groups: six cats received injection of the dye in two different sites: right cranial thoracic mammary gland, and left cranial abdominal mammary gland; whereas seven other cats were inoculated with the dye in two other sites: right caudal thoracic mammary gland, and left caudal abdominal mammary gland.

Lymphadenectomy

For axillary ipsilateral LN lymphadenectomy, cadavers were positioned in dorsal decubitus, and thoracic limbs were stabilized for proper visualization of axillary site. The axillary site was divided by surgical marker (Texta®) into three portions (cranial, middle, and caudal) (Figure 2).

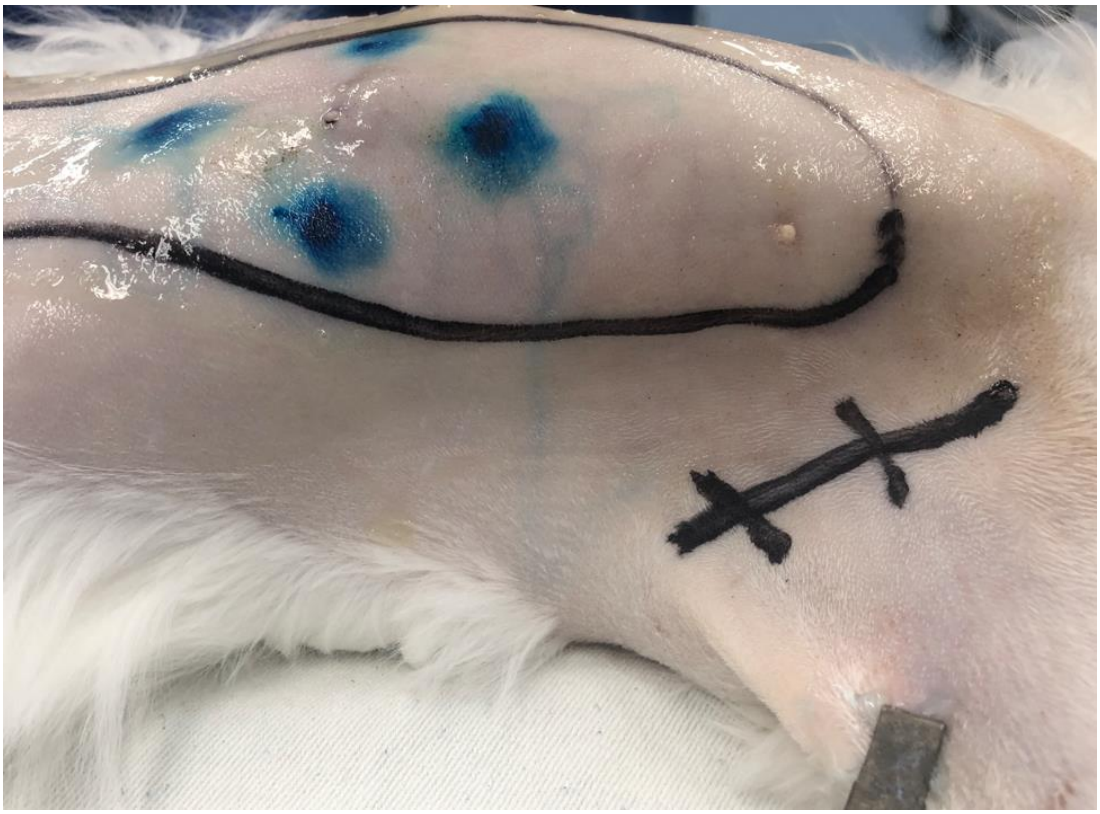

Figure 2. Intradermal injection sites of patent blue dye in the cranial thoracic mammary gland (dark blue) and the anatomical division of the feline axilla into three segments for initial skin incision prior to axillary lymphadenectomy (black). The image also depicts the dye-filled lymphatic vessels (light blue) connecting the cranial thoracic mammary gland to the axillary region.

Subsequently, a skin incision was made in the central portion of the armpit, followed by divulsion of the subcutaneous tissue and incision of the deep pectoral muscle, allowing the identification of the axillary LN(s) adjacent to the *teres major* muscle, between the lateral thoracic and axillary arthery and veins, on the medial aspect of the arm. The lymphatic and blood vessels were ligated with 3-0 polyglecaprone-25 suture material (Bioline®) in the hilum of the LN. Muscle and subcutaneous sutures were performed with the same material, approaching distant muscle fibers in a simple continuous pattern, followed by suture of the dead space in the same suture pattern, and the skin in a simple interrupted suture with 3-0 nylon (Shalon®). Contralateral axillary LNs were not assessed. For superficial inguinal ipsilateral LN lymphadenectomy, pelvic limbs were stabilized for proper visualization of the inguinal site. A skin incision was made in the caudal third of the retro umbilical region of the abdomen, immediately after the inguinal mammary gland, with further divulsion of the subcutaneous tissue, and exposure of the LN(s), followed by ligation of the vessels with 3-0 polyglecaprone-25 (Bioline®), and removal of the observable node(s). In sequence, a simple continuous suture reduced dead space with the same absorbable suture material, and then the skin was sutured with a simple interrupted pattern, using 3-0 nylon (Shalon®). Contralateral superficial inguinal LNs were not assessed. The assessment of LNs was based on patent blue visual staining, counting, size, and location. Subsequently, samples were submitted for histopathological evaluation.

Histological processing

Following surgical removal, samples were fixed with 10% neutral buffered formalin solution and were forwarded for standard histological processing. Upon fixation, specimens were grossly evaluated regarding measurements and corticomedullary distinction on cut section. Then, representative sections were included in histological cassettes following the sample identification: sample code + anatomic site where dye was applied (e.g. right cranial thoracic mammary gland, left cranial abdominal mammary gland, right caudal thoracic mammary gland, and left caudal abdominal mammary gland).

Tissue sections (4 µm) were submitted to deparaffinization in xylene solution, rehydration in graded alcohol, and rinsing in water, followed by standardized hematoxylin-eosin staining, as described by Luna (1968), with minor modifications. Photomicrographs were taken using a light microscope (Opticam O500R).

Statistical analysis

Descriptive statistical analysis was conducted, and all gathered data, encompassing LN count, size, and location, was compiled into an Excel® spreadsheet (Microsoft Corp.). The most frequent sentinel LN and variations of normal lymphatic drainage found were evaluated through the chi-square test in order to analyse the frequency dispersion of LNs that received lymphatic drainage, following administration of 2.5% patent blue dye. For that, we used the software GraphPadPrism v. 6.02 and considered a significance level of 5%.

RESULTS

The total number of animals submitted to the study was 13 female cats. Ages ranged from 2 to 14 years (mean of 5 ± 3.3 years); weight ranged from 2 to 5.3 kg (mean of 2.5 ± 1.3 kg) and all cats had no defined breed. A total of 32 LNs stained with patent blue were identified: 16 right axillary LNs, 2 left axillary LNs, 2 left superficial inguinal LNs, and 12 right superficial inguinal LNs. All tissues collected were reviewed histologically, as shown in Figure 1.

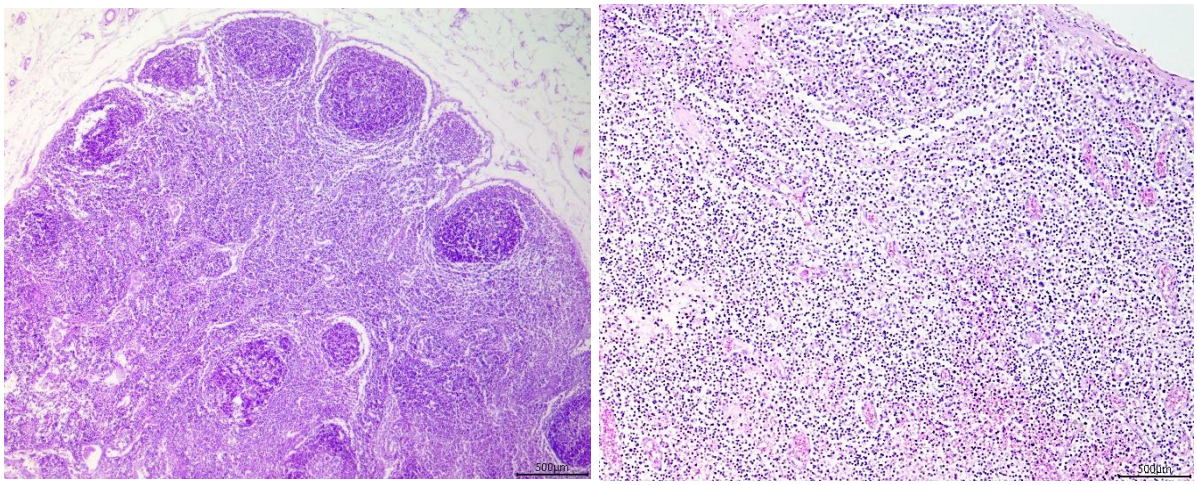

Figure 3. Histological features of lymph nodes previously dyed with patent blue dye in cats. (A) Lymph node, unremarkable. Note the lymphoid follicles evenly distributed within the superficial lymphoid cortex (top). Hematoxylin and eosin (HE), 40x. (B) Lymph node with corticomedullary sinuses. HE, 400x.

The median size of the 18 axillary LN identified was 0.2 cm (mean of 0.24 ± 0.1 cm), while for the 14 superficial inguinal LN confirmed, the median size was 0.3 cm (mean of 0.32 ± 0.09 cm). The weight of cats and their LNs' size were tested for Pearson's correlation. A moderate positive correlation was observed between the individual's weight and the size of the superficial inguinal lymph node (R= 0.4608; p= 0.0972). Similarly, a positive moderate correlation was also identified between the weight of the cat and the size of the axillary LNs (0.4578; p= 0.0560).

Twelve cats (92.3%) had overt lymphatic drainage from the administration site to their respective lymph center. However, one cat had no lymphatic drainage after dye administration for any of the tested anatomic sites.

Information regarding absolute and relative frequency values for each lymphatic site is included in Table 1 alongside with the corresponding mammary gland site following dye application.

Table 1. Lymph nodes retrieved from mammary gland regional sites after 2.5% patent blue dye in cats, and frequency of drainage.

Mammary gland*	Cases	Lymph node	Frequency of drainage
Cranial thoracic (right)	5	Axillary LN	100% (5/5)
Caudal thoracic (right)	7	Axillary LN	71.4% (5/7)
		Axillary LN + Superficial inguinal LN	28.5% (2/7) (p = 0.109)
Cranial abdominal (left)	5	Superficial inguinal LN	80% (4/5)
		Axillary LN + Superficial inguinal LN	20% (1/5) (p = 0.058)
Caudal abdominal (left)	7	Superficial inguinal LN	100% (7/7)

* Anatomic site in which the vital dye was administered intradermally.

Following the administration of dye into the cranial thoracic mammary gland, the identification of right axillary LNs displayed a variability ranging from one to two, wherein three out of five cats (60%) exhibited the presence of one LN, while two out of five cats (40%) presented two axillary LNs. These axillary LNs exhibited sizes of 0.1 to 0.3 cm (mean ± standard deviation: 0.2 ± 0.05 cm). In one patient, the application of patent blue dye to the region of the cranial thoracic mammary gland did not result in the detection of lymphatic drainage.

Upon the administration of patent blue dye into the right caudal thoracic mammary gland, subsequent drainage into the right axillary LNs yielded similar variability, with one to two LNs identified per cat. Specifically, five out of seven cats (71.4%) demonstrated the presence of one axillary LN, while two out of seven cats (28.6%) exhibited two LNs in the right axillary region (p = 0.109). The size of these right axillary LNs ranged from 0.2 to 0.4 cm, with a mean size of 0.26 ± 0.11 cm. These LNs were consistently located between the 3rd and 4th intercostal spaces, positioned beneath the deep pectoral muscle. Notably, all identified axillary LNs displayed a round morphology and firm consistency.

Additionally, upon intradermal administration of the dye into the right caudal thoracic mammary gland (Figure 4), two cats displayed the identification of one right inguinal LN each. These inguinal LNs measured 0.3 cm in size, exhibited an elongated

configuration, possessed a firm texture, and were situated adjacent to the right external pudendal artery and vein.

Figure 4. Identification of the axillary lymph node following the administration of 2.5% patent blue in a female cat. The image demonstrates the stained axillary lymph node (dark blue) and the cranial thoracic mammary gland (light blue). The patent blue dye allowed for clear visualization of the lymph node, emphasizing the dye's effectiveness in lymph node identification.

Upon the administration of patent blue dye to the left cranial abdominal mammary gland, a consistent pattern of drainage to a single left inguinal lymph node (LN) was observed across all cases. The size of these inguinal LNs exhibited a range from 0.2 to 0.4 cm, with a mean size of 0.3 cm ± 0.06 cm. These superficial inguinal LNs consistently displayed an elongated shape and firm consistency and were consistently situated caudally to the left external pudendal artery and vein.

Furthermore, when patent blue dye was administered to the left cranial abdominal mammary gland, it resulted in ipsilateral drainage to two left axillary lymph nodes, but this was observed in only one cat. Both of these axillary LNs measured 0.2 cm, displayed a round shape, and exhibited firm consistency.

Application of the dye to the left caudal abdominal mammary gland led to the identification of a single left inguinal LN in all animals. The size of these inguinal LNs varied from 0.2 to 0.6 cm, with a mean size of 0.34 cm ± 0.11 cm. Similar to the previous cases, these inguinal LNs exhibited an elongated shape and firm texture.

DISCUSSION

Peritumoral intradermal administration of 2.5% patent blue dye is indicated for LN visualization at doses of 2mg/kg, not exceeding the volume of 1 ml per patient (CASSALI et al. 2020). After injection, the dye drains through the lymphatic system, allowing visualization of the lymphatic vessels surrounding the administration tissue and the LN. The advantages of this method include high detection rates of LNs by blue staining, simplicity in performing the technique, the quickness of dye drainage, and low cost (BIANCHI et al. 2018, PIMENTEL et al. 2024, PINHEIRO et al. 2003). We observed and confirmed those benefits throughout the course of the experiment.

As the lymphatic system ceases to function after death, the technique of applying 3% hydrogen peroxide proved to be an efficient alternative for the dilation of lymphatic vessels in this experimental model, allowing the drainage of the water-soluble dye, and can be used in studies of anatomy and surgery. The technique was performed as described by SUAMI et al. (2013), who observed that hydrogen peroxide reacts with tissue enzymes around the injection site producing oxygen gas and distending the lymphatic vessels of cadavers. The absence of draining of the dye in one cat may have occurred due to detrimental factors associated with tissue autolysis. It sustains the fact that the preservation of the cadavers directly interferes with the effectiveness of hydrogen peroxide permeability; thus, animals with advanced decomposition stages have decreased reactions (SUAMI et al. 2013).

In cats, the axillary lymphatic chain is composed of the axillary LNs (1 to 2 LNs), also called proper axillary LN, located between the 1st and 2nd intercostal space, and the accessory axillary LNs in 97% of cats, localized between the 3rd and 4th intercostal space, commonly representing two, and rarely three, LNs (RAHARISON & SAUTET 2007). In the present study, all identified axillary LNs were identified between the 2nd and 4th intercostal space, and the maximum number of lymph nodes found was two.

The inguinofemoral lymph centre is composed of the superficial inguinal LN (1 to 2 LNs), caudal superficial epigastric LN (or accessory superficial inguinal LN) found in up to 98% of cats. The cranial superficial epigastric LN, included in the ventral thoracic lymph centre, may be present in up to 7% of cats (DEZDROBITU & DAMIAN 2011, WAIBL et al. 2012). Only one inguinal LN was identified in each case, located caudally to the superficial caudal epigastric vein and adhered to the mammary gland tissue (M4).

Few anatomical investigations delineate the lymphatic drainage patterns originating from the mammary glands in feline cadavers or healthy felines (MORRIS 2013, RAHARISON & SAUTET 2007). It is crucial to recognize that lymphatic and venous drainage may exhibit variations when comparing a healthy mammary gland with one affected by a tumoral microenvironment, due to the pro-angiogenic and lymphangiogenic capabilities inherent to tumor cells (PATSIKAS et al. 2006, SLEECKX et al. 2014). These observed alterations highlight the need for sentinel LN mapping in the context of malignant neoplasms in cats (CHITI et al. 2022).

In cats, under physiologic conditions, the thoracic mammary gland (M1) drains only to the axillary LN (RAHARISON & SAUTET 2007). However, the caudal thoracic

mammary gland (M2) may also drain to the superficial inguinal LN, as presented in our study, in 28.5% (2/7) cases. In a study conducted with 27 cases and using black India ink (0.25 cm^3) for LN drainage, 23% of cases of M2 drained to the inguinal LN. Similarly, the cranial region of the cranial abdominal mammary gland (M3) drains to the axillary lymph node, while its caudal region, along with the abdominal mammary gland (M4) drains to the inguina LN (GIMÉNEZ et al. 2010, RAHARISON & SAUTET 2007). In this study, only 20% of cases (1/5) of M3 drained to the axillary LN, while previous study presents a higher rate of 65% (RAHARISON & SAUTET 2007).

Lymphatic communication between the contralateral mammary glands has not been proven. Nonetheless, contralateral local infiltration of MGTs in cats has previously been documented (GIMÉNEZ et al. 2010). Therefore, in cases of neoplasia in these mammary glands, both LNs should be removed (axillary and inguinal).

Studies examining mammary lymphatic drainage are more common in female dogs than in female cats. A study that analysed 44 LNs in bitches, identified 90.9% (40/44) of axillary LNs after patent blue dye administration via the subpapillary route in dogs undergoing mastectomy (PINHEIRO et al. 2003). Another study found 95.9% (47/49) of the axillary LNs using the same peritumoral dye, also in the presence of MGTs (BIANCHI et al. 2018). Some factors might determine the success rate of sentinel LN identification, such as the surgeon training, and the occurrence of false negatives due to lymphatic blockage due to the formation of emboli or mechanical compression in the case of large tumors (PIMENTEL et al. 2024, QUADROS & GEBRIM 2006).

Among mammary neoplasms in cats, adenocarcinomas are the most common histological type, also subdivided into carcinoma *in situ*, solid carcinoma, tubulopapillary carcinoma, and cribriform carcinoma among others (CASSALI et al. 2020, DE CAMPOS et al. 2016). There is no difference among biological behaviour between histopathological subtypes, although grade is decisive for biological behaviour and aggressiveness. Metastatic rates are among 50% to 90%, and the LNs are the main metastatic sites, followed by lungs and liver (PETRUCCI et al. 2021). The presence of metastases represents a significant cause of morbidity and mortality in in cats, dogs and women with MGTs (CASSALI et al. 2020). According to the modified clinical staging classification of the WORLD HEALTH ORGANIZATION (WHO), cats are classified in stage III in the presence of tumors larger than 3 cm or with metastasis in a regional lymph node, and IV in the presence of distant metastases (BORREGO et al. 2009). Hence, determining the status of the sentinel lymph node is crucial for accurate staging in cats with MGTs. Recently it has been advocated a recommendation of bilateral radical mastectomy in two stages, with excision of the axillary and inguinal LNs ipsilaterally to the tumor in cats with MGTs (GEMIGNANI et al. 2018). However, given its aggressiveness, each case should be assessed individually, considering factors such as the patient's age, prognosis, life expectancy, quality of life, and associated comorbidities.

Regarding limitations, our sample size was smaller than anticipated due to the strict inclusion and exclusion criteria imposed. We designed these criteria to enhance the reliability of our results by focusing on individuals with intact tissues and minimal disruption of the normal lymphatic drainage, thereby reducing the influence of

abnormalities, such as those seen in the presence of neoplasms. While our primary objective was to identify axillary and superficial inguinal LNs, it is worth noting that other LNs might also play a role in neoplastic lymphatic drainage of mammary gland tissue however, their importance to tumor spread is still not well understood in cats. Although using the same cadaver for two pattern analyses of LN drainage is not ideal, given the absence of contralateral lymphatic drainage according to literature and the limited sample size, we agreed to proceed with this approach in our study.

CONCLUSION

This research has provided additional evidence regarding the dual drainage pattern of the caudal thoracic mammary glands and the cranial abdominal mammary glands in cats, which occurs both cranially through the axillary lymph nodes and caudally through the superficial inguinal lymph nodes, even in the absence of MGTs. It highlights the functional significance of both the axillary and superficial inguinal lymph nodes in mammary gland lymphatic drainage. Given that the caudal thoracic and cranial abdominal mammary glands exhibit a higher likelihood of draining to multiple regional lymph nodes, the presence of neoplasms warrants a thorough assessment. This includes evaluating the potential need for lymphadenectomy in both regional lymph centers, as is typically considered in radical mastectomy procedures.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, and formal analysis**, Thais Coelho Lopes, Pedro Antônio Bronhara Pimentel, Roselene Ecco and Rodrigo dos Santos Horta**; software and validation**, Rodrigo dos Santos Horta;** investigation**, Thais Coelho Lopes and Rodrigo dos Santos Horta**; resources and data curation**, Carlos Eduardo Bastos Lopes, Roselene Ecco and Rodrigo dos Santos Horta**; writing-original draft preparation**, Thais Coelho Lopes and Rodrigo dos Santos Horta**; writing-review and editing**, Pedro Antônio Bronhara Pimentel and Rodrigo dos Santos Horta**; visualization**, Pedro Antônio Bronhara Pimentel and Rodrigo dos Santos Horta**; supervision, **Rodrigo dos Santos Horta**; project administration, **Rodrigo dos Santos Horta**; funding acquisition, **Rodrigo dos Santos Horta**. All authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable for studies not involving humans or animals.

INFORMED CONSENT STATEMENT

Not applicable because this study did not involve humans.

DATA AVAILABILITY STATEMENT

The data can be made available under request.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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